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Survey

Functional activities of the human T-cell leukemia virus type I Tax oncoprotein: cellular signaling through NF-κB

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Abstract

Human T-cell leukemia virus type I (HTLV-I) is the etiological agent for adult T-cell leukemia (ATL), as well as for tropical spastic paraparesis (TSP) and HTLV-I associate myelopathy (HAM). A biological understanding of the involvement of HTLV-I and in ATL has focused significantly on the workings of the virally-encoded 40 kDa phospho-oncoprotein, Tax. Tax is a transcriptional activator. Its ability to modulate the expression and function of many cellular genes has been reasoned to be a major contributory mechanism explaining HTLV-I-mediated transformation of cells. In activating cellular gene expression, Tax impinges upon several cellular signal-transduction pathways, including those for CREB/ATF and NF-κB. In this paper, we review aspects of Tax's transcriptional potential with particular focus on recent evidence linking Tax to IKK (IκB-kinase)-complex and MAP3Ks (mitogen-activated protein kinase kinase kinases). Published by Elsevier Science Ltd.

Keywords: HTLV; Adult T-cell leukemia; Cellular transformation; NF-κB; Tax; CREB; AP-1; HAM/TSP

Contents

1. HTLV-I and adult T-cell leukemia (ATL)

Human T cell leukemia virus type 1 (HTLV-I) is the etiological agent for adult T cell leukemia (ATL) [1],

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tropical spastic paraparesis (TSP) and various neurological disorders termed HTLV-I-associated myelopathy (HAM) [2]. While the linkage between TSP/HAM and HTLV-I is less understood, the role of HTLV-I in ATL has been well-investigated. In this regard, in vivo, ATL cells show nuclei with morphological aberrations (indented or lobulated; [1]) and abnormal karyotypes [3,4]; in particular, trisomy of chromosomes 3 and 7, as well as deletions and breaks in chromosome 6 have been observed [5–8]. ATL cells frequently present as pleiomorphic multinucleated giant cells [9,10]. Consistent with in vivo findings, lymphocytes infected in vitro with HTLV-I show profound chromosomal changes [11,12] verifying a link between viral infection and morphological changes in infected cells.

While it is not yet fully understood how HTLV-I engenders ATL, several lines of evidence link the virally encoded 40 kDa nuclear phosphoprotein [13], Tax, to cellular transformation [14–19]. Thus, Tax has been shown to immortalize T lymphocytes [20] and transform rat fibroblasts [14]. Tax not only sufficiently initiates the immortalization and transformation of human thymocytes, cord blood lymphocytes and murine fibroblast cells in vitro [14,16,20], but in some settings has been shown to function in maintaining the transformed phenotype [21]. Tax-transformed fibroblast and lymphoid cells induced tumors in vivo when injected into nude mice [14,21,22]. Interestingly, overexpression of HTLV-1 Tax in transgenic mice resulted in the formation of mesenchymal tumors [23], salivary and lacrimal gland exocrinopathy [24], lympadenopathy or splenomegaly [25] and lymphoma or leukemia [26]. Finally, when Tax is deleted from the HTLV-I genome, this altered proviral molecule is lost for its original transforming potential [27].

Mechanistically, the role of Tax in cellular transformation likely relates to its activity as a transcriptional activator. Tax potently stimulates the expression of its cognate viral LTR [28,29], as well as the promoters of several cellular genes. Thus, cellular genes such as IL-2, IL-2R, *c-fos*, GM-CSF [19,30–38], as well as β-polymerase, *c-myb*, *Lck* and p53 [39–43] have all been shown to be influenced by expression of Tax in cells.

In understanding Tax's pleiotropic transcriptional activities, work from several laboratories have collectively defined its ability to act through four discrete cellular signaling pathways: CREB/ATF [44]; NF-κB [45]; AP-1 [46]; and SRF [47] (Fig. 1). Amongst these pathways, Tax's signaling through CREB/ATF and NF-κB has been most extensively investigated. Here, we review in brief our current understanding of Tax's transcriptional activity, with particular emphasis on recent findings pertaining to its signaling through NF-κB. For further discussions of these topics, readers are encouraged to consult several excellent recent reviews [45,48,49].

2. Nuclear transcriptional activities of Tax

The HTLV-I Tax protein is predominantly a viral nuclear antigen [50] with a well-defined nuclear localization signal (NLS; [51]) found in its N-terminal 48 residues. Despite this, it is evident that a small amount of Tax protein resides in the cytoplasm of mammalian

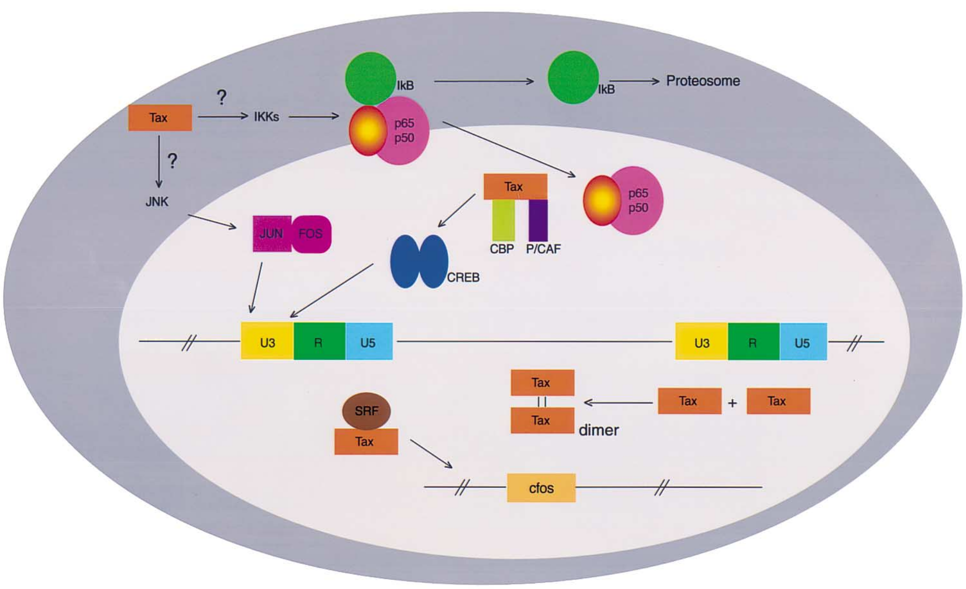

Fig. 1. Schematic representation of the nuclear and cytoplasmic functions of HTLV-I Tax protein. Tax is shown to activate IKK- and JNK-signaling pathways in the cytoplasm. The IKK-pathway impinges on the nuclear migration of NF-κB (p50p65 heterodimer); the JNK-pathway leads to activation of Jun/Fos. In the nucleus, Tax is envisioned to dimerize and to interact with CREB, CBP and P/CAF co-factors as well as with SRF in activating gene transcription. Tax-responsive elements in the HTLV-I LTR reside within the U3.

cells [52]. Thus, in modulating gene expression, Tax is envisioned to have promoter–poximal (i.e. nuclear) as well as promoter–distal (i.e. cytoplasmic) effects (see Fig. 1). Initial studies on Tax demonstrated convincingly that despite its abundant nuclear presence, Tax by itself cannot associate directly with DNA [44]. Contemporaneous findings, however, provided clear evidence that Tax could deregulated the expression of several cellular immediately early (IE) genes. This Tax-mediated dysregulation of gene expression is believed to contribute importantly to its abrogation of normal cellular metabolism [53].

2.1. SRF and AP-1

An early clue as to how HTLV might affect cellular IE genes emerged from the finding that the DNA-binding serum responsive factor (SRF; [54]) could recruit the Tax protein to cellular promoters such as those for *c-fos*, *egr-1* and *egr-2* [47]. Thus, the $CC(AT)_6GG$ motif (CarG box)-binding SRF protein was found to be necessary for Tax's transcriptional activation of a limited subset of promoters [55]; and residues 422–435 of SRF was defined to bind Tax directly [56]. Hence, one mechanistic view is that CarG-box-tethered SRF would bind Tax, thereby bringing the viral oncoprotein to the promoter. The C-terminal activation domain of Tax [57] is then thought to contact directly with TATA-box bound TBP-protein [58] resulting in enhanced transcription.

Many cellular IE genes also contain promoter upstream AP-1 sites. Several studies have shown that HTLV-I transformed T-cells express high levels of AP-1 activity [59,60]. Interestingly, the canonical AP-1 responsive sequence (5′TGACTCA3′) bears close resemblance to the three imperfectly conserved core cAMP-responsive palindrome (5′ TGACGTCA; [61]) present in the Tax-responsive 21-bp elements found in the HTLV-I LTR. Direct experimental studies have demonstrated that the 21-bp Tax-responsive elements can serve as Jun-responsive sequences [46]. Subsequent work has confirmed that Tax can activate the expression of several cellular promoters through AP-1 sites [62,63]. Despite these reports, currently, it remains unclear whether the major mechanism guiding Tax-activation through AP-1 is via a promoter–proximal enhancement of the DNA-binding activity of AP-1 [64,65], or through a Tax-mediate activation of the JNK-1 kinase [66]. Relevant to the latter possibility, a Tax-binding protein which signals through the TNF-α/AP-1 pathway has recently been described [67].

2.2. CREB, CBP, P/CAF

The HTLV-I LTR (long terminal repeat) contains three imperfectly conserved 21 bp Tax-responsive (TxRE) sequences, each of which contains a core CREB/ATF binding sites flanked by 5′G- and 3′C-rich residues [29,68]. Highly efficient activation of this viral LTR by Tax is, in part, explained by Tax/CREB/TxRE ternary complex formation at these sites in the LTR [69–73]. However, the ability of Tax to activate transcription via CREB/ATF-sites is context specific, since at other CREB-binding sites (i.e. those found in cellular promoters), Tax–CREB complex formation may occur [70,74,75], but transcriptional activation is not seen.

While the exact details of how Tax activates transcription through CREB/ATF is not completely understood, several findings which contribute important mechanistic insight have been established. It is proposed that the N-terminus of Tax (Fig. 2) directly binds CREB molecules [69,75] docked at CRE-sites in the viral TxRE. Binding of Tax to CREB enhances CREB–CREB homodimerization and heightens resulting association to DNA ([76]; Fig. 3). Because optimal activation through TxREs requires a dimeric form of Tax-protein [77,78], enhanced CREB-dimerization at the HTLV-I LTR could result as a functional consequence of Tax–Tax homodimerization (Fig. 3).

In the Tax/CREB/TxRE ternary complex, Tax makes limited direct contact with DNA [79–81] through its 89–110 amino acid residues ([82]; Fig. 2). Contact with DNA is suggested to result in proper folding of the Tax protein [82] that may lead to a functional presentation of its C-terminal activation domain [57]. Correctly folded Tax protein is known to recruit through its amino acid residues 81–95 ([83]; Fig. 2) the transcriptional co-activators, CBP and p300 ([84–86]; Fig. 3). However, recruitment of CBP/p300 was found to be insufficient for supporting Tax's transcriptional activity [83], suggesting that an additional necessary component for activity remained uncharacterized. This missing factor could be the p300–CBP associated factor, P/CAF, which was recently shown to bind to the C-terminal activation domain of Tax ([87,88]; Figs. 2 and 3). Indeed, Tax mutants that fail to bind to P/CAF correlate with the loss of ability to activate transcription from the HTLV-I LTR [87].

3. Signaling by Tax through NF-κB

The biology of ATL cells is characterized by increased expression of genes coding for lymphokines [12,19,89] and lymphokine receptors (e.g. IL-2Rα; [19,30–32]). Expression of these genes is in part regulated by the NF-κB family of transcription factors. The NF-κB family encompasses several related proteins [90], which can homo- or hetero-dimerize in binding to a GGGRNNYYCC DNA-motif. NF-κB family members function pleiotropically in diverse aspects of immune/inflammatory responses and cellular growth and differ-

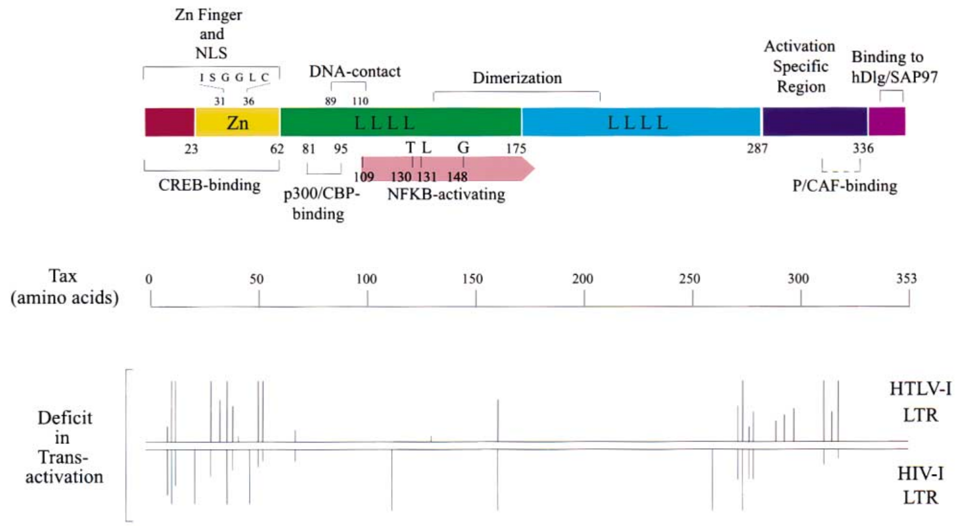

Fig. 2. Linear representations of the various functional domains which have been characterized for the 353 amino acid Tax protein. (Top) The N-terminus of Tax contains a nuclear localization signal (NLS) and a zinc-finger (Zn) structure. CREB-binding domain within Tax has also been mapped to the N-terminus. An 'ISGGLC'-sequence has been suggested to contact CREB2 [154]. p300/CBP, P/CAF and DNA-contact domains are indicated. The middle of Tax contains several Leucine (L) residues and is necessary for homodimerization and for NF-κB activation [155]. At its C-terminus, Tax has an activation domain and a sequence specific to Tax1, but absent from Tax2, which binds to the tumor suppressor hDlg/SAP97 [156]. (Bottom) Schematic representation of single amino acid Tax mutants [94] which were characterized for deficit in transactivation of either the HTLV-I (CREB/ATF pathway) or the HIV-1 (NF-κB pathway).

entiation [91]. Early HTLV-I research found, interestingly, that Tax activation of genes, such as that for IL-2Rα, occurred through NF-κB binding sites [92,93]. Subsequently, extensive mutagenesis studies [94,95] supported the idea that Tax can generally activate cellular transcription through a NF-κB-dependent pathway in a manner distinct from its activation of CREB/ATF (Fig. 2). This concept is compatible with the observation that NF-κB activity is constitutively elevated in primary adult T-cell leukemia cells as well as in Tax-expressing cells [96–100].

3.1. Interaction of Tax and NF-κB in the nucleus

NF-κB family members include p105, p100, p65, p52, p50, c-Rel and Rel B [90]. The most frequently observed NF-κB form is that of a p50–p65 dimer, which is ambiently retained in the cytoplasm by inhibitor ankyrin repeat-containing IκB molecules (IκBα, IκBβ, IκBε, p105, p100 and Bcl-3; reviewed in Ref. [101]). In the commonly accepted paradigm, IκBα and IκBβ play major roles in sequestering p50–p65 dimer in the cytoplasm. Upon activation of cells by mitogens, cytokines, bacterial lipopolysaccharides, virus infection and/or stress signals, induced-phosphorylation of IκBα and IκBβ occurs on serines 32 and 36 and serines 19 and 23, respectively (reviewed in Ref. [91]). Phosphorylated IκBα and IκBβ subunits are then targeted by ubiquitin-ligase component protein, β-TrCP (reviewed in Ref. [102]); this interaction leads to the ubiquination and proteosomal degradation of the IκBs. Upon removal of IκBs, NF-κB-molecules are freed to migrate from the cytoplasm into the nucleus. Within the nucleus, NF-κBs bind promoter upstream DNA-motifs and activate the transcription of a diverse subset of target genes.

Because of Tax's predominant nuclear localization in cells, an initial mechanistic explanation for Tax–NF-κB interplay invoked events within the nucleus. In this regard, Tax and NF-κB proteins were observed by immunomicroscopy to colocalize together [103] within nuclear bodies that contain RNA polymerase II and other transcription factors [104]. Tax was also found to capably bind NF-κB subunits p50 [105] and p52 [106], suggesting a role in direct enhancement of NF-κB's nuclear transcription function. More recent studies have indicated that the primary action of Tax is to affect NF-κB signaling in the cytoplasm (see below). However, when cytoplasmic signaling events were inhibited by the use of dominant negative mutants, a small residual activation of NF-κB by Tax could still be observed [107]. Hence, currently, it cannot be completely excluded that in HTLV-I infected cells nuclear interactive events co-operate with the cytoplasmic effects of Tax to influence overall NF-κB activation.

3.2. Tax and cytoplasmic signaling of NF-κB

There are two perspective as to how cytoplasmic Tax modulates NF-κB activity. Previously, it was known that Tax could directly bind the ankyrin motif contained in molecules such as cyclin-dependent kinase inhibitor $p16^{INK4A}$ [41,108,109]. Such observation sup-

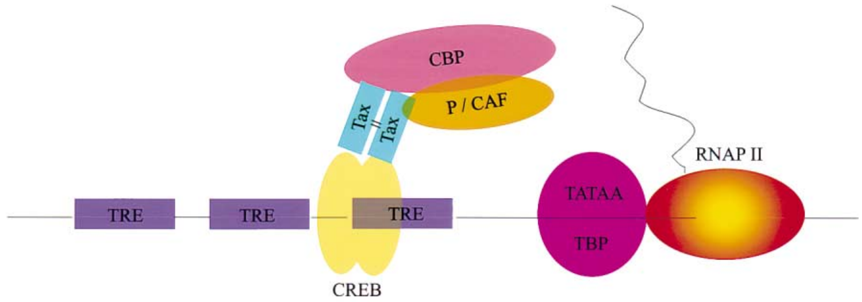

Fig. 3. A model of Tax-mediated transcription through the CREB/ATF pathway. A CREB-dimer is shown to bind to the Tax-responsive elements (TRE) and interact with a Tax homodimer capable of recruiting a molecule(s) of CBP/p300 and P/CAF. This CREB/Tax/CBP/(P/CAF) complex can then influence TATAA-bound TATA-binding protein (TBP) to enhance the initiation of RNA-polymerase II (RNAP II).

ported the reasoning that Tax might physically contact IκB-molecules through similar ankyrin-motifs, thereby dissociating IκBs from cytoplasmically sequestered NF-κBs (Fig. 4A). This idea proposes a contact-dependent dissociation mechanism through which Tax would target IκBs for proteosomal degradation [110]. Compatible with this view, Tax was found to associate with both IκBα [111–113] and p105 [114], which can function as a cytoplasmic IκB-molecule. However, subsequent studies using Tax and IκBα mutants defined clearly that direct contact between these two molecules insufficiently explains NF-κB-activation (reviewed in Ref. [45]) suggesting the existence of an alternative activating mechanism(s).

Besides the dissociation model of IκB from NF-κB, another general mechanism of NF-κB activation describes site-specific phosphorylation of IκBα, followed by its ubiquitination and degradation [115–117]. A plethora of studies have defined IκB phosphorylation as a critical regulatory step for NF-κB activation. Recent insights into how IκBα phosphorylation occurs inside cells were revealed from extensive characterizations of a 700-kDa complex which contains kinase activity specific for serine 32 and 36 of IκBα [118,119]. Detailed analyses of this large-kinase-complex resulted in the cloning of two IκB-kinases — IKKα and IKKβ [120–124]. IKKα is an 85-kDa protein, while IKKβ is an 87-kDa protein. Both are 52% identical and contain an N-terminal kinase domain, a leucine zipper and a helix-loop-helix motif. Using purified recombinant IKKα and IKKβ, it was unambiguously proven that these kinases specifically phosphorylated IκBα and IκBβ with a slight preference for the former over the latter [125].

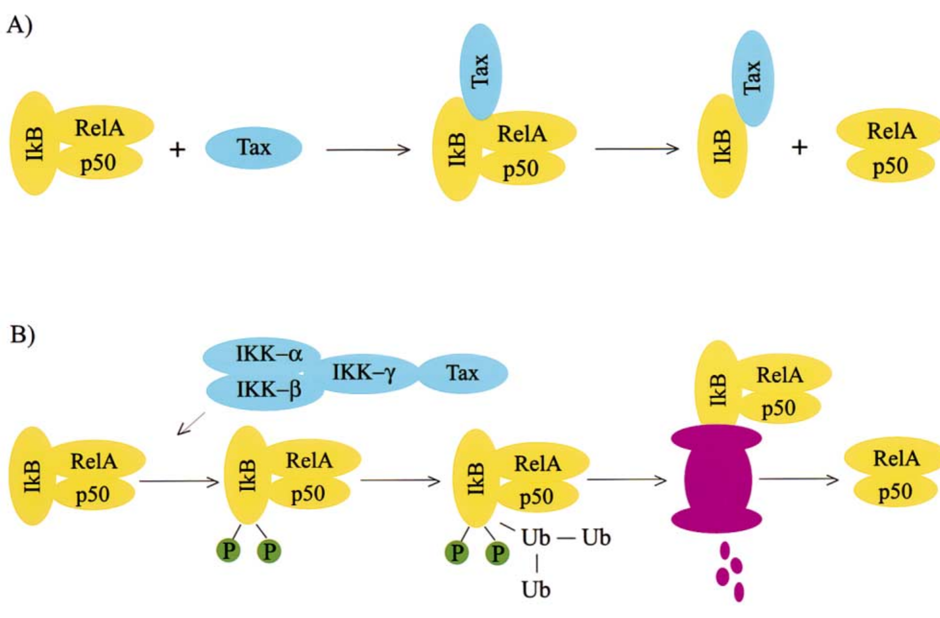

Fig. 4. Two models explaining Tax-mediated 'freeing' of NF-κB from IκB sequestration. (A) Direct contact of Tax with IκB leads to dissociation of IκB from NF-κB (RelA/p50). (B) Tax is recruited to IkB/NF-κB complex through IKKα/β/γ. In this scenario, a Tax-dependent MAP3K activity (not shown) is envisioned to phosphorylate IκB leading to its ubiquination and degradation by proteosome.

The large intracellular IKK-α and IKK-β containing-complex, interestingly, was also found to include two members of the MAP kinase kinase kinase (MAP3K) group, MAPK/ERK kinase kinase 1 (MEKK-1) and NF-κB-inducing kinase (NIK) [126–129]. Very recently, a non-catalytic regulatory subunit for the IKKα and IKKβ named IKKγ (or NEMO) was also identified in this complex. cDNAs for human and mouse IKKγ have been cloned [130–132]. Collectively, based on the work of several independent laboratories, it is currently understood that in virtually all settings activation of either IKKα or IKKβ requires the IKKγ subunit, since mouse cells deficient in IKKγ fail to phosphorylate and degrade IκBs and do not activate NF-κB in response to diverse stimuli such as TNFa, IL-1, LPS and double-stranded RNA [131]. It is additionally understood that both IKKα and IKKβ are activated by phosphorylation on specific serines (S176 and S180 for the former; S177 and S181 for the latter). In this regard, NIK [127,128] and MEKK1 [126,128,129], as well as additional MAP3Ks [133,134] have been invoked as IKK-activating kinases (IKKK). Intriguingly, despite these advances, it remains controversial as to which MAP3K represents the authentic intracellular IKKK needed to activate NF-κB (reviewed in Refs. [135,136]).

In the context of the IKK-signalosome, how does Tax function mechanistically to activate NF-κB? Biochemically, over-expressed Tax protein was found by several investigators to be present within the large IKKα-[137–139] and IKKβ-[137–140] containing intracellular complex. An initial interpretation was that perhaps Tax contacted either IKKα or IKKβ proximally. However, subsequent findings verified that it is IKKγ that binds Tax directly. Thus, IKKγ functionally adapts the Tax-oncoprotein into the large IKKα/IKKβ/IKKγ complex [40,141,142].

Simultaneous with the physical characterizations of IKK-Tax association, complementary functional studies have clarified as to how IKK-α and IKK-β activities might be impinged upon by Tax (Fig. 5). First, it was found that dominant negative forms of NIK inhibited Tax-activation of NF-κB [138,139]. This suggested that Tax acts at a step upstream of NIK-phosphorylation of IKKα/β. Next, work from Gaynor et al. demonstrated a direct association between MEKK1 and Tax, which resulted in a preferential activation of IKKβ [140]. A dominant negative form of MEKK1 was shown by these investigators to also inhibit Tax-activation of NF-κB [140]. Together, these results propose a redundant usage of multiple MAP3Ks by Tax for NF-κB-activation. Consistent with this redundancy, we have recently observed that over-expression of a dominant negative form of MLK3 (another MAP3K; [134]) further inhibited independently NF-κB activation by Tax [143]. The molecular interplays between these MAP3Ks

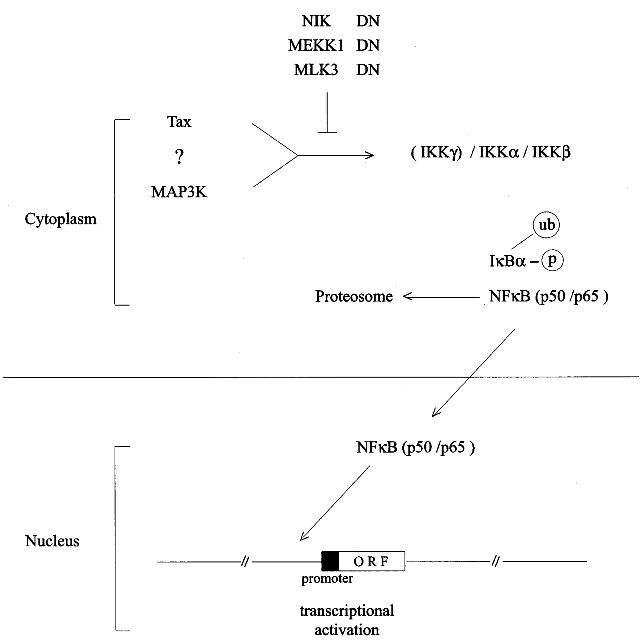

Fig. 5. Summary of sequential events in Tax-activation of nuclear NF-κB activity. A not yet fully understood interaction occurs between Tax and a MAP3K in the cytoplasm. The identity of the relevant MAP3K remains controversial, although dominant negative forms of NIK, MEKK1 and MLK3 all independently suppress Tax-activation of NF-κB. Tax is then recruited into the IKKα/β/γ complex. Parenthesis around IKKγ indicates that Tax activation of NF-κB remains intact in at least one cell line deficient for IKKγ, suggesting that other factors may substitute for IKKγ. The IKK/Tax/MAP3K complex is then postulated to phosphorylate IκBα. Phosphorylation of IκBα triggers a ubiquitin-proteosomal degradation pathway which frees NF-kB (p50/p65) to migrate into the nucleus.

and whether additional MAP3Ks can be utilized by Tax remain to be investigated.

How might one then coalesce extant observations on Tax activation of NF-κB through the IKK-complex? While several questions remain to be answered, the following statements seemingly describe a plausible functional scenario (Fig. 5). Tax activation of NF-κB occurs at a point down-stream of the small G proteins and the TNF-α receptor interacting factors [138,140]. At this juncture, Tax bridges the IKK-complex with a MAP3K. Evidence for this bridging mechanism is supported by evidence of direct contact between Tax and both IKKγ [40,141,142] and MEKK1 [140]. MAP3K, as recruited by Tax, is then speculated to phosphorylate IKKα/β leading to a cascade of events (reviewed in Refs. [91,101]) which releases NF-κB for nuclear migration (Fig. 5). This paradigm is compatible with most of our existing findings on Tax and NF-κB.

Several important issues regarding NF-κB activation in HTLV-I-infected cells are, however, not addressed by the above scenario. First, in light of recent findings from knock-out mice that MEKK1 might be dispensible for NF-κB activation [144], the authentic intracellular MAP3K utilized by Tax requires further definition.

Second, the fact that the gene encoding for IKKγ resides on the X-chromosome [132] suggests IKK-γ functions to be sex-biased [145,146]. Alternatively, there could be additional yet recognized adapter proteins that redundantly serve the IKKγ-function. Indeed, in support of this supposition, a B-precursor-cell line, genetically deficient for IKKγ, was previously shown to support fully Tax-activation of NF-κB [147]. Understanding what are the additional IKKγ-like proteins that could be functionally used by Tax represents a compelling future challenge. Third, additional IKKγ-binding protein [148] which influence NF-κB-activation has recently been identified. It would be of interest to clarify how such protein(s) might influence the biology of Tax–IKK interaction. Finally, whether Tax alone explains in vivo NF-κB activation within HTLV-I infected cells has been recently questioned by investigators [100]. The observation that constitutive NF-κB activation exists in HTLV-I infected cells that do not detectably express Tax suggests that additional virally-encoded (induced) factors should also be carefully investigated [100].

4. Implications for cellular transformation

A critical reason for investigating Tax–NF-κB interaction is to understand the contribution of this pathway to cellular transformation. Several studies support that Tax activation of NF-κB contributes to transformation [149–151]. On the other hand, two other studies have suggested that activation through the CREB/ATF pathway by Tax plays a more important role [20,152]. Most recently, experiments using the HTLV-II Tax (Tax2) protein have provided an elegant explanation for these discrepancies. Green et al. demonstrated that NF-κB-activation by Tax2 provided for initiation of transformation while CREB/ATF-activation served necessarily to maintain the transformed phenotype [153]. An important future goal would be to elucidate how these two pathways cooperate in the important biological process of cellular transformation.

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